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The Albright Syndrome Associated With Acromegaly: Report of a Case and Review of the Literature

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Abstract The association of the Albright syndrome (polyostotic fibrous dysplasia of bone, hyperpigmented skin macules, and endocrine disorders) with acromegaly has been infrequently substantiated. The case of an 18-year-old girl with the classic Albright syndrome and acromegaly is described. The patient had a history of coarsening of acral and facial features, an insulin-resistant form of diabetes mellitus and elevated fasting growth hormone values. Neuro-endocrine studies demonstrated failure of growth hormone to suppress to less than 5 ng/ml during an oral glucose tolerance test, and the abnormal release of growth hormone upon injection of thyrotropin-releasing hormone. Although L-dopa failed to decrease growth hormone levels, bromocriptine produced a modest decline in growth hormone within two hours of ingestion. The patient had also experienced secondary amenorrhea with sub-normal follicle-stimulating-hormone (FSH) and luteinizing hormone (LH) levels, both of which demonstrated a prolonged sluggish response to an injection of gonadotropin-releasing hormone (GnRH); this response suggested hypogonadotropic hypogonadism, possibly on the basis of a tumor involving both pituitary and hypothalamus. Sellar polytomography demonstrated an enlarged sella with dorsal erosion and an asymmetric floor. Computerized tomography of the brain visualized a suprasellar mass extending into the hypothalamus. These findings suggest a hypersecretion of hypothalamic releasing factors, pituitary hormones, or both as an etiology for the endocrinopathy in this patient, and lend support to the theory that the endocrinopathies associated with the Albright syndrome result from over-production of hypothalamic-releasing hormones or autonomous secretion of pituitary hormones from an adenoma.

INTRODUCTION

The Albright syndrome consists of the triad of polyostotic fibrous dysplasia of bone, hyperpigmented skin macules, and a wide variety of endocrinopathies including isosexual precocity (1–3), hyperthyroidism (4), the Cushing syndrome (5, 6), hyperparathyroidism (1, 7, 8), and, occasionally, acromegaly (9–12). Albright himself stated: "It might be wiser only to describe the condition and not to try to come to any conclusion concerning its etiology and the relation of one manifestation to another." (13) Since that statement was made, there has been little progress in determining the etiology of the endocrinopathies. Two opinions currently prevail: 1) that the endocrinopathies are the result of hypothalamic hypersecretion of releasing hormones (14), and 2) that the involved endocrine organs are unduly sensitive to trophic hormones (2) or act in an autonomous fashion (6, 15). To date, very few cases of the Albright syndrome with well-documented pituitary or hypothalamic lesions have been reported. We describe here a young woman having the classic Albright syndrome and acromegaly with a mass involving both the hypothalamus and pituitary. We also review the literature concerning the association between acromegaly and the Albright syndrome.

CASE REPORT

An 18-year-old white woman was referred to The Johns Hopkins Hospital for evaluation of acromegaly. She was the product of a normal, full-term vaginal delivery. During the first year of life an enlarged cranium was noted, and a congenital dislocation of the left hip was corrected. Also, an irregular hyperpigmented macular area on the lower back had been noted at birth. At age 2 bilateral pathologic fractures of the fibulae occurred. By age 6, congenital nerve deafness had been identified, and a third kidney was revealed by intravenous pyelography during an investigation for repeated urinary tract infections. At age 8, a maxillary bone growth was removed

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and diagnosed histologically as fibrous dysplasia. At that age, she also underwent reconstruction of the right maxilla and orbit to correct optic nerve impingement secondary to fibrous dysplasia. A similar procedure was performed at age 10. A year later she underwent bilateral wedge resections of the femurs to realign her lower extremities. At age 15 and again at age 17 right orbital and maxillary surgery was required to prevent optic nerve damage and malalignment of the upper jaw. During childhood and adolescence, pathologic fractures involving the right clavicle, bilateral tibiae, and the left femur occurred and were attributed to fibrous dysplasia.

Menarche, thelarche and adrenarche occurred at age 9, but her periods were irregular throughout adolescence, occurring only once every six months and lasting for only two days. The diagnosis of the Albright syndrome was made on the basis of the classic triad of precocious puberty and the dermatologic and osseous findings.

From ages 16 to 18, the patient gained 125 pounds (increasing in weight from 135 to 260 pounds) despite dieting, and was continually hungry. At age 18, non-insulin–dependent diabetes mellitus was diagnosed by a routine laboratory test, and the patient was placed on a regimen of chlorpropamide, 250 mg daily. There were no complaints of polyuria, polydypsia, or episodes of ketosis, but she was troubled by frequent urinary tract infections, vaginal moniliasis and cellulitis of the right calf. During this time she noted an increase in hand and shoe size and coarsening of her skin. Additionally, she had amenorrhea from age 17 to 18. She denied having headaches, visual or voice changes, acne, galactorrhea or increase in body hair. She was referred to an endocrinologist who found that she had basal growth hormone levels of 12 ng/ml which did not suppress to normal (<5 ng/ml) during an oral glucose tolerance test. Tomography of the sella was alleged to show enlargement consistent with a pituitary tumor, and the patient was referred to The Johns Hopkins Hospital for evaluation of acromegaly.

The family history was significant for a father with nephrolithiasis and a maternal grandmother with an unspecified thyroid disorder; a brother, age 17, had undergone normal growth and development. The patient had always done well in school and is currently enrolled as a freshman in a college which specializes in teaching the deaf.

On physical examination, blood pressure was 120/85 mmHg, pulse was 80/min and regular, weight was 235 pounds, and height was 5 feet, 7¼ inches. She was an obese, deaf, white woman with coarse facial features. Pertinent physical findings included a 15 × 4 cm irregular café-au-lait spot on the right buttock, and two 5 × 5 cm spots near the right sacrum (Fig 1); coarse thick skin with increased soft tissue in both hands; multiple well-healed surgical scars involving both lower extremities and upper lip; an enlarged cranium with a widened right orbital ridge; a space between the upper molars; protrusion of the upper gums; a slightly enlarged symmetric thyroid; extensive internal and external vaginal moniliasis with external post-inflammatory hyperpigmentation; 1+ pretibial edema; and absent Achilles tendon reflexes bilaterally. There were no abnormal funduscopic findings, and breast development was normal. No galactorrhea was present.

Initial laboratory studies showed a normal complete blood count; electrolytes and SMA 12 were also normal except for an alkaline phosphatase level of 197 IU/L (normal, <119 IU/L). Urinalysis showed specific gravity 1.020, 2+ protein, 2+ glucose, negative acetone, 0 to 2 white blood cells and 0 to 2 red blood cells per high power field, and budding yeast. The patient's electrocardiogram showed left atrial abnormality, and her chest x-ray demonstrated hypoinflation and kyphosis. Bilateral hand films were compatible with a diagnosis of fibrous dysplasia and showed diffuse deformity of the left distal radius, right distal ulna and bilateral metacarpals and phalanges with numerous small cysts. Bilateral foot films showed similar findings with a well-healed fracture of the right third metatarsal. Skull films suggested thickening of the sphenoid and basisphenoid. Fibrous dysplasia involved the sphenoid sinus, the anterior and posterior clinoids and the clivus (Fig 2). Polytomography of the sella turcica demonstrated an asymmetrical sella floor with right-sided depression and erosion of the dorsum sellae. Sella volume was estimated at 2,000 cc (normal, approximately 1,150 cc). A computerized tomographic scan of the brain demonstrated an enlarged sella and a suprasellar mass (Fig 3).

Endocrine Evaluation

Hormonal evaluation included a T_4 level of 5.8 μg/dl (normal, 4.5–11.5); T_3 resin uptake 28.2% (normal, 25–35); TSH 1.8 μU/ml (normal, <8); 24-hour urine free cortisol 35 μg/24 hr (normal, 15–75 μg/24 hr); and baseline prolactin 21 ng/ml (normal, <22). Tables I and II summarize further endocrine testing of growth hormone dynamics, and demonstrate an elevated fasting growth hormone; non-suppressibility of growth hormone with oral glucose; release of growth hormone with an injection of thyrotropin-releasing hormone (TRH); a small increase in growth hormone with oral L-dopa; and a modest decline in growth hormone levels with oral bromocriptine. Table III shows results of a gonadotropin-releasing hormone (GnRH) test which demonstrates

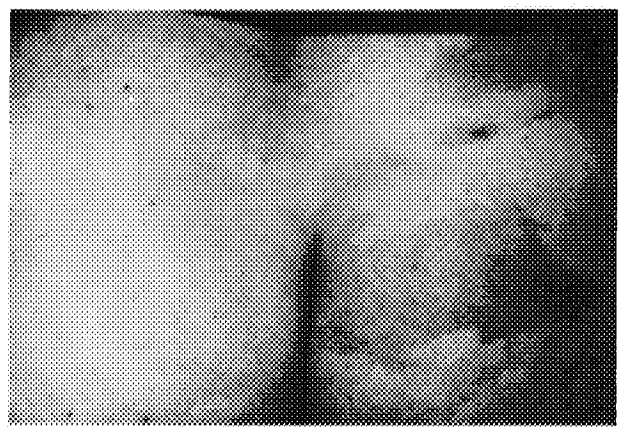

Fig 1. Multiple typical "coast of Maine" nevi on back and buttocks of patient.

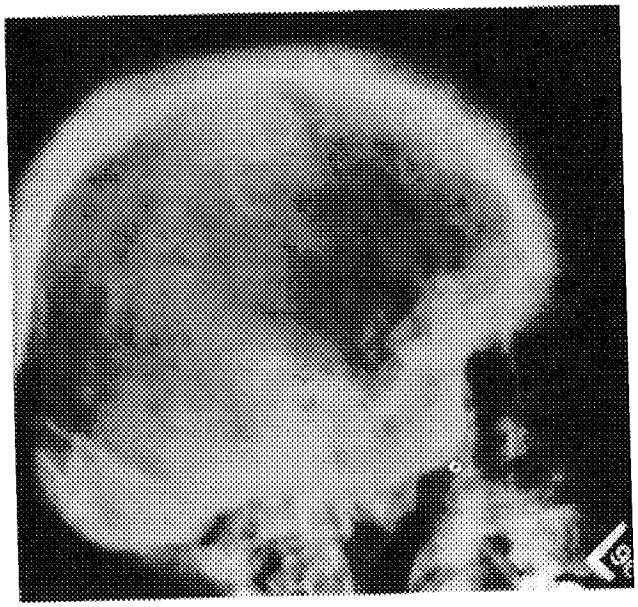

Fig 2. Skull radiograph showing extensive involvement of the cranium with polyostotic fibrous dysplasia and distortion of the sellar region.

subnormal basal gonadotropins and a sluggish subnormal response of FSH and LH to the injection of GnRH.

The patient declined further work-up and was examined one year later at The George Washington University Medical Center. During that year she experienced gradual weight gain, continuation of the mild glucose intolerance, and the onset of mild diastolic hypertension in the range of 95 to 100 mmHg. Results of repeat sella polytomography and computerized scanning of the brain were unchanged and again demonstrated erosion of the sella and a suprasellar mass. Goldmann visual fields revealed several small bilateral paracentral and nasal scotomas attributable to prior orbital impingement by

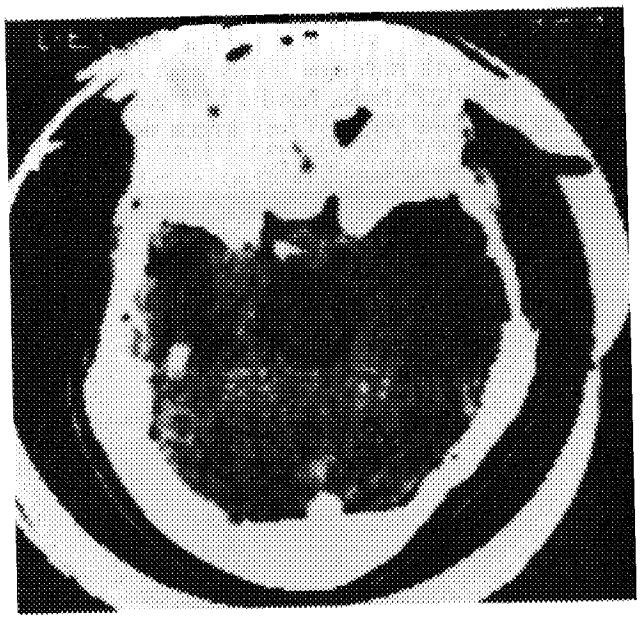

Fig 3. Computerized tomographic scan of the brain showing a suprasellar lesion extending into the hypothalamus.

TABLE I

Effect of Oral Glucose Tolerance Test on Growth Hormone Levels

Time (Minutes)	0	60	90	120	180	300
Glucose (mg/dl)	265	465	474	482	396	299
Growth hormone (ng/dl)*	29	12	13	13	18	15

* Normal <5.0 ng/dl

the Albright disease. No temporal field defects or scotomas were noted. A repeat oral glucose tolerance test elicited results similar to the study done one year previously and again demonstrated high growth hormone levels that were not suppressible with a glucose load. Measurement of 24-hour urine free cortisol was again normal, as were repeat thyroid function tests and a fasting prolactin level. A 24-hour urine test for vanillylmandelic acid, catecholamines, and metanephrine was normal. A neurosurgical consultation was obtained, and it was decided that a surgical approach would be difficult owing to the severe thickening of the cranium and sphenoid bones by the fibrous dysplasia. The patient was apprised of all possible therapeutic modalities and agreed to a course of 5,000 rads of external radiotherapy to the sella and suprasellar regions. Several months have elapsed since she received this course of treatment; she has tolerated it without complication, although her basal serum growth hormone levels have not yet returned to normal.

DISCUSSION

Although many endocrinopathies have been described in conjunction with polyostotic fibrous dysplasia of bone, there are very few well-documented reports of acromegaly complicating this condition. Many of the earlier reports, such as those by Lichtenstein and Jaffe (16), Falconer and Cope (17), Mogensen (18), and others (19, 20) were based solely on clinical observation and occurred in an era when growth hormone levels could not be measured, and sophisticated radiologic techniques for evaluation of the sella turcica were not available. Even some recent reports of acromegaly in association with the Albright syndrome are poorly substan-

TABLE II

Effect of Thyrotropin-Releasing Hormone (TRH), L-Dopa, and Bromocriptine on Growth Hormone Levels

Time (Minutes)	0	15	30	45	60	90	120
Growth hormone (ng/dl) (TRH 500 μg I.V.)	16.1	26.5	20.4	17.3	13.1		
Growth hormone (L-Dopa 500 mg P.O.)	11.7		14.7		15.1	15.3	16.6
Growth hormone (Bromocriptine 5.0 mg P.O.)	21.3		19.2		17.3	17.2	16.1

TABLE III

Effect of Gonadotropin-Releasing Hormone (GnRH) on Gonadotropin Levels*

Time (Minutes)	0	30	105	135	265
FSH†	46	80	112	123	140
LH‡	5	19	24	17	21

* 100 μg I.V.
† Normal (follicular phase): 261 ± 81 ng/ml
‡ Normal (follicular phase): 57 ± 21 ng/ml

tiated, being based on clinical appearance rather than neuroendocrine evaluation (21). The bone deformities in advanced polyostotic fibrous dysplasia can result in a distortion of facial features which mimics or can be confused with the acromegalic appearance (22). Also, optic nerve involvement from the bone disease can result in visual field abnormalities similar to those seen with an expanding pituitary tumor (23).

To date, only five well-documented cases of acromegaly in association with the Albright syndrome have been described. Scurry et al. (9) in 1964 were the first to note the presence of an abnormally elevated growth hormone level in a patient with the Albright syndrome, acromegalic features and sella polytomographic abnormalities consistent with a pituitary tumor. Lightener et al. (10) observed a child with polyostotic fibrous dysplasia, gigantism, and elevated growth hormones which were not suppressed by glucose loading or chlorpromazine. At surgery, a large eosinophilic pituitary adenoma with suprasellar extension was found (24). Similarly, Joishy et al. (11) described a patient with a chromophobe pituitary adenoma and non-suppressible growth hormone levels and gigantism. A less well-defined patient with abnormally elevated growth hormones is discussed in the Polish literature (12), and recently a patient with the Albright syndrome, galactorrhea, hyperprolactinemia and non-suppressible growth hormone was reported (25). The latter patient had been managed on a regimen of bromocriptine, with resolution of the galactorrhea, but no follow-up growth hormone evaluation was described.

The patient under discussion has many of the classic physical features of the Albright syndrome and some early clinical signs of acromegaly. Additionally, she had an insulin-resistant non-ketotic form of diabetes mellitus, similar to the type occasionally seen with acromegaly (26). The neuro-endocrine evaluation which had been performed supported the clinical diagnosis of acromegaly. The results included an elevated basal fasting growth hormone (27); failure to suppress growth hormone to less than 5 ng/ml with an oral glucose load (28, 29); and release of growth hormone in response to a TRH injection (30). Although L-dopa may cause a decline in growth hormone levels in some acromegalic patients (31), such a response was not seen in our patient. Bromocriptine, however, reduced the growth hormone level modestly at 2 hours in this patient. This type of response has been described previously in acromegalic patients (32). Prior research (33) suggests that it is possible that a further decline in growth hormone levels would have been observed if measurement of growth hormone levels had been carried out for an additional two to four hours. In fact long-term treatment of acromegalic patients with bromocriptine has led to a significant fall in growth hormone levels in over half of the cases (34).

The patient's baseline gonadotropin levels were subnormal for the follicular phase of the menstrual cycle and responded sluggishly to GnRH. Moreover, the maximal response of LH and FSH to GnRH occurred considerably beyond the normally expected time for peak elevations, and the peaks were far less than normally observed (35). These findings suggest that the tumor was interfering with gonadotropin release, synthesis, or both. It is likely that this hypogonadotropic state was a major factor in the patient's amenorrhea. Also, her sudden weight gain and marked increase in appetite were possibly attributable to derangement of the hypothalamic centers controlling eating behavior and satiety.

The visual field abnormalities noted in this patient, however, were less likely to be due to the pituitary tumor. They were more typical of field defects seen secondary to orbital infringement by the polyostotic fibrous dysplasia, a problem which had necessitated several surgical corrective procedures in this patient.

This patient's growth changes, abnormal growth hormone dynamics, and a suprasellar mass lesion as demonstrated by computerized axial tomography leave little doubt of the diagnosis of acromegaly. This case addresses the controversy regarding the underlying etiology of these endocrinopathies associated with the Albright syndrome. Certainly the data presented here favor a central cause for the endocrinopathy, that is, oversecretion of growth hormone or various neurotransmitters and hypothalamic releasing factors which increase growth hormone secretion. This view is in line with the hypothesis of Hall and Warrick (14), and suggests that an overproduction of hypothalamic-releasing factors is a possible cause of the endocrinopathies. Although others have hypothesized that the syndrome is a result of end-organ hormonal autonomy (15) or increased sensitivity of the end-organs to the trophic hormones (2), there are little data to support these theories in the patient under discussion.

There is support, however, for end-organ autonomy in many previously-described patients. These include patients with the Albright syndrome who were reported to have the Cushing syndrome secondary to adrenal hyperplasia (5, 6) and young women with low gonadotropins, elevated estrogens, and precocious puberty (2). The hyperthyroidism of the Albright syndrome is always associated with low or undetectable TSH levels, and most patients have multi-nodular goiters rather than the typical findings of Graves disease (4). In view of the diversity of endocrinopathies associated with this syndrome neither the central hypothalamic theory nor the

theory of end-organ autonomy fully explains the origin of the endocrine disorders in all cases of the Albright syndrome. Possibly, as DiGeorge (15) has suggested, the Albright syndrome represents a new form of multiple endocrine neoplasia based on a genetic marker or cell line common to all involved tissues, or an as-yet-undefined stimulating factor acting on all involved organs. Albright himself suggested such a theory in his original work when he stated: "... It is possible that the whole syndrome represents some embryologic defect affecting multiple systems." (13) At present, no unifying concept exists to explain all of the different endocrine abnormalities seen in association with this disorder.

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